

REMARKS

Claims 1, 3-27 and 29-41 are presently pending in this application. Claims 3, 4, 16-26, 29, 31-34 and 36-41 have been withdrawn by the Examiner as being drawn to non-elected inventions.

Claims 3, 4, 29 and 36-41 have been canceled, without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in one or more related application.

Claim 1 has been amended to add the proviso that the body tissue is not conditioned by nutrient deficiency. Support for the proposition that claims can be properly amended to exclude one or more species of a genus when the specification provides a generic disclosure of the genus and numerous species within the genus, including the species being excluded from the scope of the claim, can be found in *In re Johnson*, 558 F.2d 1008, 1019, 194 U.S.P.Q. 187, 196 (C.C.P.A. 1977) (*see also* Manual of Patent Examining Procedure, Eighth Edition, Revision 6, September 2007, § 2173.05(i) at page 2100-223). Here, the specification provides a generic disclosure of methods for conditioning the body tissue, including biological conditioning, chemical conditioning, pharmaceutical conditioning, physiological conditioning and mechanical conditioning (see page 12, lines 22-24), and also provides disclosures of numerous species within each conditioning method (see pages 14-24), including nutrient deficiency (see page 22, lines 20-21). According to *In re Johnson*, claim 1 can be properly amended to exclude nutrient deficiency as a method for conditioning the body tissue.

Claim 13 has been amended to delete the recitation of "RGD." New claim 42 has been added to recite the subject matter deleted from claim 13. Support for the new claim can be found in the specification at, *inter alia*, page 8, lines 2-3.

Claim 35 has been amended to recite that steps (a) and (b) are conducted before the harvesting in step (c). Support for the amendments can be found in the specification at, *inter alia*, page 3, lines 28-29.

Claims 1, 27 and 35 have been amended to insert "a" before "body tissue" when recited in the first instance.

No new matter has been added. Upon entry the present amendments, claims 1, 5-27 and 30-35 and 42 will be pending in this application.

I. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

Claim 13 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that claim 13 is considered indefinite since it recites a broad range or limitation “cell binding domain” together with a narrow range or limitation “RGD” that falls within the broad range or limitation.

In response, Applicants have amended claim 13 to delete the recitation “RGD.” Thus, the rejection is obviated and should be withdrawn.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 1, 5, 9 and 11-14 are rejected under 35 U.S.C. § 102(b) (“Section 102(b)”) as allegedly being anticipated by Vituri *et al.* (Brazilian Journal of Medical and Biological Research 33:889-895, 2000).

Claim 35 is rejected under 35 U.S.C. § 102(e) (“Section 102(e)”) as allegedly being anticipated by Mitchell *et al.* (US 2002/0115208).

1. The Legal Standard

An anticipating reference must describe and enable the claimed invention, including all the claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. *In re Spada*, 911 F.2d 705, 708, 15 U.S.P.Q.2d 1655, 1657 (Fed. Cir. 1990); *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375, 62 U.S.P.Q.2d 1917, 1921 (Fed. Cir. 2002). The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987): “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989) (holding that “[t]he identical invention must be shown in as complete detail as is contained in the...claim”). Further, the anticipating reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.* 75 F. 3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996).

**2. Amended Claim 1 and Its Dependent Claims
Are Not Anticipated By Vituri *et al.***

In the Office Action, the Examiner alleges that Vituri *et al.* anticipates claims 1, 5, 9 and 11-14, since Vituri *et al.* discloses that bone marrow extracellular matrix (ECM) from undernourished mice had greater amounts of extractable fibronectin and laminin compared to control animals (see page 4, last paragraph). Although Applicants disagree, solely to expedite prosecution and obtain coverage for certain embodiments of the presently claimed invention, Applicants have amended claim 1 to recite that the body tissue is not conditioned by nutrient deficiency. As discussed above, support for the amendment can be found on page 22, lines 20-21. See *In re Johnson*, 558 F.2d at 1019.

Vituri *et al.* does not teach or suggest conditioning a body tissue by any method other than nutrient deficiency (*i.e.*, low-protein diet). As such, amended claim 1 and its dependent claims, including claims 5, 9 and 11-14, are not anticipated by Vituri *et al.*

3. Amended Claim 35 Is Not Anticipated By Mitchell *et al.*

In the Office Action, the Examiner alleges that Mitchell *et al.* anticipates claim 35, since tissue engineered constructs produced at least in part by culturing the tissue *in vivo* are contemplated by Mitchell *et al.* (see page 6, ¶1). Although Applicants disagree, solely to expedite prosecution and obtain coverage for certain embodiments of the presently claimed invention, Applicants has amended claim 35 to recite that, among other things, the conditioning in step (a) occurs before the harvesting in step (c).

Mitchell *et al.* discloses methods for producing tissue engineered constructs by growing cells *in vitro* on a substrate and then decellularizing the construct (see Abstract, lines 1-5). Mitchell *et al.* also discloses that during any of the growth phases required for the production of the construct, the construct may be subjected to various tissue engineering steps such as application of mechanical stimuli (see Abstract, lines 10-14). Mitchell *et al.* further discloses that the “construct is distinguished from an explant of a corresponding natural tissue, e.g., a native tissue, in that *the primary growth of the construct occurs in vitro*” (see page 4, [0052] at lines 8-11) (emphasis added). Accordingly, the method of Mitchell *et al.* requires the conditioning step to occur during the growing step, which occurs *in vitro*, and thus, the conditioning step must occur after the tissue is harvested.

On the contrary, amended claim 35 requires conditioning the tissue before the tissue is harvested. Thus, Mitchell *et al.* teaches away from the method of amended claim 35 and does not anticipate amended claim 35.

For the foregoing reasons, Applicants respectfully request withdrawal of the Section 102(b) and Section 102(e) rejections.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1, 5, 8-15, 27 and 35 are rejected under 35 U.S.C. § 103(a) ("Section 103(a)") as allegedly being unpatentable over Naughton (US 5,830,798) in view of Mitchell *et al.* (US 2002/0115208), Patel *et al.* (US 7,087, 089) and Wolff *et al.* (WO 99/55379).

Claims 13 and 30 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naughton in view of Mitchell *et al.*, Patel *et al.* and Wolff *et al.* as applied to claims 1, 5, 8-15 and 27, and further in view of Herlyn *et al.* (WO 98/39035).

Claims 6 and 7 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naughton in view of Mitchell *et al.*, Patel *et al.* and Wolff *et al.* as applied to claims 1, 5, 8-15 and 27, and further in view of Schwarz *et al.* (US 6,656,916).

1. The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; *see also* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Federal Register, Vol. 72, No. 195, October 10, 2007, pages 57527-57528. The Supreme Court also stated that it is "important to identify a reason that would have prompted

a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does....” *KSR*, 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396.

**2. Amended Claims 1, 27 and 35 and Their Dependent Claims
Are Patentable Over The Cited References**

In the Office Action, the Examiner briefly describes the teachings of Naughton (see page 7, ¶2 to page 8, ¶2), Mitchell *et al.* (see paragraph bridging pages 8 and 9), Patel *et al.* (see page 9, ¶2), and Wolff *et al.* (see page 9, ¶3), and alleges that “it would have been obvious for an ordinary skilled artisan in the art to modify the method of Naughton by also preparing a decellularized bone marrow extracellular matrix material harvested from the bone marrow of a donor animal, including a human donor, whose parenchymal cells of the bone marrow have been transfected with a polynucleotide encoding a protein of interest in light of the teachings of Mitchell *et al.*, Patel *et al.* and Wolff *et al.*” (see paragraph bridging pages 9 and 10). For the following reasons, Applicants disagree.

First, the Examiner used hindsight reconstruction to pick and choose among isolated disclosures in the prior art to arrive at the presently claimed invention. This is improper when one of ordinary skill in the art would have no reason to combine the teachings of the references. *See In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). The Supreme Court in *Teleflex Inc.* stated that it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does....” 127 S.Ct. at 1741.

In the present case, one of ordinary skill in the art would have no reason to combine the teachings of Naughton with any one of Mitchell *et al.*, Patel *et al.* and Wolff *et al.*, since the references each employ different body tissues and/or different techniques to achieve different objectives. For example, Naughton discloses culturing cells on a biocompatible three-dimensional framework *in vitro* (see Abstract) and genetically modifying the cells prior to expanding the cells on the framework (see col. 10, line 59 to col. 11, line 14); whereas Mitchell *et al.* discloses seeding cells on a substrate to form a tissue engineered construct (see page 7, [0081] at lines 11-14) and applying certain physical stimuli (*e.g.*, mechanical or electrical) during the growth periods (see page 9, [0096] at lines 9-22). A person of ordinary skill in the art would have no reason to substitute the genetic conditioning step in Naughton with the physical conditioning step in Mitchell *et al.*, since different conditioning steps

require different materials and methods and would have different effects on the cells. Without further guidance, a combination or substitution of conditioning steps from these references would lead to unpredictable results.

The conditioning step in Naughton also differs from that of Patel *et al.* In particular, Naughton discloses conditioning cells on a framework outside of the body (*i.e.*, *in vitro* or *ex vivo*). On the other hand, Patel *et al.* suggests the use of transgenic animal as a source of conditioned cells. Transgenic animals are produced *in vivo* or *in situ*, and cannot be separately grown on a three-dimensional framework. Therefore, one of ordinary skill in the art would have no reason to use the transgenic animal of Patel *et al.* in the conditioning step of Naughton.

Naughton and Wolff *et al.* each uses different materials in their respective conditioning step. The method of Naughton conditions human stromal cells (see Abstract) that comprise fibroblasts derived from adult or fetal tissue (see col. 7, lines 64-66). In contrast, the method of Wolff *et al.* conditions parenchymal cells (see Abstract). Wolff *et al.* explicitly states that parenchymal cells are different from cells of the connective tissue and exclude fibroblasts (see page 7, lines 16-20), and thus teaches away from the stromal cells of Naughton. Based on the teaching of Wolff *et al.*, a person of ordinary skill in the art would reasonably expect stromal cells and parenchymal cells to be structurally and functionally different and would each require a different approach for conditioning and culturing. Thus, the person of ordinary skill in the art would have no reason to apply the delivery process of Wolff *et al.* to the stromal cells used in the methods of Naughton.

Second, Applicants submit that the teachings of Naughton is complete for its intended purposes and, thus, a person of ordinary skill in the art would have no motivation to use any additional references, let alone three secondary reference, *i.e.*, Mitchell *et al.*, Petal *et al.* and Wolff *et al.*, to modify the teachings of Naughton. *In re Herschler*, 591 F.2d 693, 200 U.S.P.Q. 711 (C.C.P.A. 1979).

The Court of Customs and Patent Appeals addressed a similar situation in *In re Herschler*, when it held that the Board had wrongly rejected the appealed claims as obvious. In *In re Herschler*, the applicant taught the use of dimethyl sulfoxide (DMSO) to enhance transdermal penetration of a number of compounds, and claimed the process of applying to the skin a mixture comprising DMSO and a physiologically active steroid. 591 F.2d at 695, 200 U.S.P.Q. at 712. The Board rejected the claims as obvious over a primary reference (the

Lubowe patent), which disclosed a hair lotion containing an estrogenic hormone and a solubilizing agent other than DMSO, combined with a secondary reference (Faust), which taught that DMSO is a safe and effective solubilizing agent for cosmetic or dermatologic use. The CCPA reversed the Board's rejection on the grounds that disclosure of the primary reference was already complete for its intended purpose, so that one of ordinary skill in the art would not have been motivated to use the DMSO of the secondary reference.

Similar to the Lubowe patent, the disclosure of Naughton is complete for its intended purpose, namely a method for producing naturally secreted extracellular matrix comprising the steps of conditioning a body tissue and allowing the conditioned body tissue to produce a biological material (in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning). Because the solution is complete, Naughton provides no reason to look to the art for alternative steps to condition the cells, and, in particular, no motivation to look to the transgenic animal of Patel *et al.*, the physical conditioning of Mitchell *et al.*, and the polynucleotide delivery system of Wolff *et al.*

Furthermore, none of the cited references, either alone or together, teach or suggest each and every element of the rejected claims. As acknowledged by the Examiner (see Office Action, page 8, ¶2), Naughton does not teach or suggest conditioning a body tissue and culturing the conditioned body tissue prior to or before harvesting the conditioned body tissue, as recited in independent claims 1, 27 and 35. None of Mitchell *et al.*, Patel *et al.* and Wolff *et al.* cure the deficiency of Naughton.

As discussed above, Mitchell *et al.* discloses conditioning a body tissue during the growth phase, which occurs *in vitro* or *ex vivo* (see page 4, [0052] at lines 8-11). In order to condition the body tissue *in vitro* or *ex vivo*, the conditioning step in Mitchell *et al.* must occur after the body tissue is harvested. This is contrary to the sequence recited in the method of claims 1, 27 and 35.

Patel *et al.* discloses harvesting renal capsules from transgenic animals (see col. 3, lines 16-17), which the Examiner equates to a pre-conditioned donor animal (see Office Action, page 9, ¶2, line 5). Patel *et al.* does not explicitly disclose all the steps of the claimed methods. At most, Patel *et al.* inherently teaches that the transgenic animal has one or more body tissue (*i.e.*, the "conditioned body tissue") which produces a biological material in an amount different than the amount of the biological material that would produce by the same body tissue of a non-transgenic animal. However, Patel *et al.* does not teach or suggest that said conditioned body tissue is the tissue which is harvested and decellularized, as required by the method of claims 1, 27 and 35. In

addition, an obviousness rejection cannot be based on inherent disclosure in a prior art reference. See *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966).

Wolff *et al.* discloses a process for delivering a polynucleotide into parenchymal cells within tissues *in situ* and *in vivo* (see page 2, lines 21-22). However, Wolff *et al.* does not teach or suggest harvesting the parenchymal cells, much less teach or suggest conditioning and culturing the cells before harvesting the cells, as recited in claims 1, 27 and 35.

Therefore, the Examiner has failed to establish a *prima facie* case of obviousness, since all the claim limitations are not taught or suggested by the cited references.

Dependent claims 5-15 and 30, which recite the limitations of claims 1 and 27, respectively, also are not obvious in view of the cited references.

As previously discussed in the Amendment filed February 21, 2006 (see pages 15-16), Herlyn *et al.* discloses a method for repairing defects and inducing vascularization in mammalian tissue by administering to the tissue a recombinant replication defective virus carrying a selected growth factor gene under operative control of regulatory sequences which direct the expression of the growth factor (see Abstract). Schwarz *et al.* describes a method of using glucocorticoid to increase the cellular expression of a gene in a biological tissue after delivery of said gene to an animal (see Abstract). Neither Herlyn *et al.* nor Schwarz *et al.* cure the deficiencies of Naughton, and their teachings are taken out of context and improperly combined with the remaining references.

For the foregoing reasons, Applicants submit that a *prima facie* case of obviousness cannot be established based on the cited references. Withdrawal of the Section 103(a) rejections is respectfully requested.

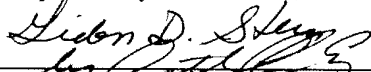
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CONCLUSION

Applicants respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

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